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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,898	03/01/2002	Alexander Olek	81658A	4523

23685 7590 09/17/2008

KRIEGSMAN & KRIEGSMAN
30 TURNPIKE ROAD, SUITE 9
SOUTHBOROUGH, MA 01772

EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/087,898	OLEK ET AL.	
	Examiner	Art Unit	
	ERIC S. DEJONG	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-31 and 35-44* is/are pending in the application.

4a) Of the above claim(s) *35-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11,13-21,23-26,28,30,31,43 and 45* is/are rejected.

7)☒ Claim(s) *12,22,27,29 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicants response filed 05/05/2008 is acknowledged.

Claims 1-3, 5-31, and 35-44 are pending. Claims 4, and 32-34 are cancelled. Claims 35-42 are withdrawn from further consideration under 37 CFR 1.142(b), as being directed to a nonelected invention, there being no allowable or generic linking claim (see applicants response, filed 10/14/2004). Claims 1-3, 5-31, 43, and 44 are currently under examination.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The rejection of claims 1-3, 5-31, 43, and 44 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 101

The rejection of claims 1-3, 5-31, 43, and 44 under 35 USC 101 as being directed to non-statutory subject matter is withdrawn in view of amendments made to the instant claims.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-11, 13-21, 23-26, 28, and 31 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Laird et al. (P/N 6,331,393 B1) in light of Klippel et al. (P/N 3,558,768).

The instant claims are drawn to a method for determining the biological effect and/or activity of at least one pharmaceutical composition comprising the steps of obtaining a biological sample A containing DNA, wherein said sample A was exposed to said at least one pharmaceutical composition, obtaining a biological sample B containing DNA, wherein said sample B was not exposed to said at least one pharmaceutical composition, subsequently analyzing the level of cytosine methylation at

chosen sites of the DNA contained in samples A and B, selecting sites which are differentially methylated between the DNA in said samples to generate a knowledge base, and concluding from said knowledge base the biological effect of said at least one pharmaceutical composition.

Laird et al. sets forth a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after treatment with sodium bisulfite (sample A; at least one pharmaceutical composition) (see Laird et al., abstract), as recited in instant claims 1, 9, and 13. Klippel et al. is further relied upon in the instant rejection to demonstrate that sodium bisulfite is a pharmaceutical composition (see Klippel et al. col. 3, line 30 through col. 4, line 36). Laird et al. disclose methylation amounts in multiple samples are quantitatively determined based on reference to a control reaction (sample B) (see Laird et al., col. 5, lines 61-64) which reads on an unexposed sample and the analysis of methylation levels in a plurality of samples, as recited in instant claims 1 and 43. Laird et al. disclose using probes and primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (see Laird et al., col. 5, lines 16-64), which reads on the selection of differentially methylated sites as instantly claimed. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as recited in instant claims 1 and 43. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e. correlation between MLH1 gene expression, MSI status, and promoter methylation

status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2 graphs of represent at least two individual rows of analyses, as recited in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as set forth in instant claim 23 (see Laird et al., col. 24, lines 48-67). Laird et al. further discloses that in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (see Laird et al., col. 1, lines 14-17), which reads on cytosine methylation as instantly claimed. Laird et al. discloses contacting a DNA sample from a patient with a modifying agent, specifically a bisulfite composition (see Laird et al., col. 5, lines 19-20 and 31), as recited in claim 44. Laird et al. further discloses various approaches to identify altered methylation sites in cancer cells (see Laird et al., col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (see Laird et al., col. 4, lines 12-15), which reads on one set of selected sites, as recited in instant claim 18. Laird et al. teaches selecting genes (see Laird et al., col. 19, line 5), which reads on a knowledge base of different classes as recited in instant claim 19. Laird et al. also discloses using PCR, sequencing, fluorescent labeling (see Laird et al., col. 7, lines 26-65), as recited in instant claim 9. Laird et al. discloses using human colorectal adenocarcinoma (cancer) and normal mucosa (healthy) tissue samples (see Laird et al., Figures 7 and 8; col. 22, lines 46-49), as set forth in instant claim 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (see Laird et al., Figure 8 and col. 8, line 64 to col. 9, line 12), which reads on at least two methylation sites selected and analyzed in parallel, as

recited in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of bisulfite-treated DNA samples (see Laird et al., col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains hypermethylatable CpG islands that undergo de novo methylation in human colorectal tissue in all normal and tumor samples (see Laird et al., col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30), which reads on methylation sites that are located in methylation relevant genes associated with cancer, as recited in instant claim 14. Laird et al. discloses using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which reads on analyzing all potential methylation sites of the DNA, as recited in instant claim 10. Laird et al. further disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then analyzing DNA samples by COBRA analysis or an amplification process using fluorescence-based real-time quantitative PCR (see Laird et al., col. 16, line 55 to col. 17, line 17), as set forth in instant claims 6-8. Laird et al. disclose that altered DNA methylation pattern of cytosine residues is mutagenic (see Laird et al., col. 2, lines 34-36) which demonstrates that the colorectal samples mentioned above represent genes associated with ulcerative colitis which is a type of colon disease, as recited in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (see Laird et al., col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et

al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen) (see Laird et al., col. 23, lines 28-37) which represents histologically, dissected biological material from healthy and diseased individuals in instant claims 2-4. Laird et al. discloses the use of paraffin embedded samples (see Laird et al., col. 9, lines 42-46). Laird et al. discloses using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (see Laird et al., col. 14, lines 5-20), which reads on the selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as recited in instant claims 20, 26, and 31.

Response to Arguments

Applicant's arguments filed 05/05/2008 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 USC 102(e)(2) as being anticipated by Laird et al. (P/N 6,331,393 B1) in light of Klippel et al. (P/N 3,558,768), applicants argue that Laird et al. has been misread as disclosing methylation amounts in multiple samples are quantitatively determined based on reference to a control reaction (sample B) and site Laird et al. col. 5, lines 61-64 as support. Applicants further argue that this cited passage states the amount of DNA in the sample is determined, not that the amount of methylation is determined and thus step c) is not carried out on this sample.

In response, it is not agreed that the Laird et al. reference has been misread as argued by applicants. Step c) of instant claim 1 recites "analyzing the level of cytosine

methylation at chosen sites of the DNA contained in the biological samples of A and B. It is maintained that the control reaction set forth by Laird et al. comprise biological samples that are exposed to varying amounts of a bisulfite composition as well as samples that are not exposed at all and thus meets the recited limitation of unexposed sample. Further, contrary to applicants argument, the further teaching of Laird et al. the quantitative "methylation amounts in nucleic acid" reads directly on analyzing the level of cytosine methylation as recited in step c) as instantly claimed. Therefore applicants argument is not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-11, 13-21, 23-26, 28, 31, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laird et al. (P/N 6,331,393 B1) in light of Klippel et al. (P/N 3,558,768) as applied to claims 1-3, 5-11, 13-21, 23-26, 28, and 31 above, and further in view of Lorincz et al. (Molecular and Cellular Biology (2000) pages 842-850).

As set forth above, Laird et al. sets forth a method for determining DNA methylation by means of treatment with sodium bisulfite that modifies DNA only at cytosines located 5' to guanosine in CpG dinucleotide islands. Laird et al. further discloses using parallel reactions with methylated, unmethylated, and control oligos with the bisulfite-treated DNA samples, and, further, the analysis of methylation events following treatment of DNA with sodium bisulfite (see Laird et al., col. 18, lines 36-39). However, Laird et al. does not expressly teach the treatment of a biological sample with at least one pharmaceutical composition followed by an analysis step requiring a separate step of treatment said biological sample with at least one of bisulfite, hydrogen sulfite, or disulfite as recited in instant claim 43.

Lorincz et al. teaches a bisulfite analysis of cells which were first treated with 5-azacytidine in order to induced GFP expression and reveal a measurable demethylation pattern (see Lorincz et al., Abstract and page 843, col. 1, lines 52-72).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the method for determining DNA methylation by treatment of biological samples with sodium bisulfite (a subsequent analysis step comprising further treatment of a biological

sample with at least one of bisulfite, hydrogen sulfite, or disulfite), as taught by Lorincz et al., to determine the methylation pattern of DNA from cells which were first treated with 5-azacytidine (biological sample exposed to a pharmaceutical composition) because Lorincz et al. expressly teaches the analysis of samples first treated with 5-azacytidine by means of a subsequent treatment with sodium bisulfite. One of ordinary skill in the art would have a reasonable expectation of success because Laird et al. teaches the disclosed methodology as an improved high throughput technique for determining methylation patterns. One of ordinary skill in the art would further recognize the predictable outcome that methylation patterns in DNA isolated from cells first treated 5-azacytidine would be readily identified via the methodology set forth by Laird et al., taught as an improved method for identifying methylated DNA sites) using sodium bisulfite treatments.

Response to Arguments

Applicant's arguments filed 05/05/2008 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 USC 103(a), applicants reiterate the previous argument directed toward Laird et al.

For the reasons provided above, applicants argument is not persuasive.

Allowable Subject Matter

Claims 12, 22, 27, and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. DEJONG whose telephone number is (571)272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S DeJong/
Primary Examiner, Art Unit 1631